Biosynthesis of Cyclic Peptide Antibiotics

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Research in the 20th century identified several large families of natural products including terpenoids, alkaloids, polyketides, and non-ribosomal peptides. The genome sequencing efforts of the first decade of the 21st century have revealed that another major class is formed by ribosomally synthesized and post-translationally modified peptides (RiPPs). These molecules are produced in all three domains of life, their biosynthetic genes are ubiquitous in the currently sequenced genomes, and their structural diversity is vast. Lantibiotics are examples of this growing class and many members are highly effective peptide-derived antimicrobial agents that display nanomolar minimal inhibitory concentrations (MICs) against pathogenic bacteria. These peptides are post-translationally modified to install multiple thioether crosslinks. During their biosynthesis, a single enzyme typically breaks 8-16 chemical bonds and forms 6-10 new bonds with high control over regio- and chemoselectivity. This seminar will discuss investigations of the mechanisms of these remarkable catalysts as well as their use for the generation of non-natural cyclic peptides.